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# APPLICATION FOR UNITED STATES PATENT

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**Title:** TRANEXAMIC ACID FORMULATIONS WITH REDUCED ADVERSE EFFECTS

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## SPECIFICATION

# TRANEXAMIC ACID FORMULATIONS WITH REDUCED ADVERSE EFFECTS

## Field of the Invention

The invention is directed to therapeutic oral tranexamic acid formulations that minimize or eliminate undesirable side effects.

## Background

Tranexamic acid (trans-4-(aminomethyl) cyclohexanecarboxylic acid, Cyklokapron® (Pfizer) is an antifibrinolytic agent. That is, it helps to prevent lysis or dissolution of a fibrin clot which forms in the normal physiologic process of hemostasis. Its mechanism of action is as a competitive inhibitor of plasminogen activation, and as a noncompetitive inhibitor of plasmin; both plasminogen and plasmin are activators of fibrinolyis and active clot-lysing agents. Tranexamic acid

thus helps to stabilize fibrin clots, which in turn maintains coagulation and helps to control bleeding.

Tranexamic acid is used to control excess bleeding, for example, excess bleeding that occurs during dental procedures in hemophiliacs and for heavy bleeding during menstruation (menorrhagia). Women suffering from menorrhagia are typically treated orally with 500mg tranexamic acid tablets administered three of four times daily with a total daily dose ranging from 3 grams/day (two tablets every eight hours) to 6 grams/day (three tablets every six hours). However, this treatment may cause adverse gastrointestinal reactions, including nausea, vomiting, diarrhea, and cramping, etc. These gastrointestinal side effects are due to the quantity of tranexamic acid introduced into the stomach with each dose, as well as the large quantity of excipients used in tablet formulation that are introduced into the stomach. Such side effects, in addition to the cramping, bloating, pain, and other symptoms that may accompany menses, are undesirable, and a formulation of tranexamic acid is needed which will reduce or eliminate these side effects.

**SUMMARY OF THE INVENTION**

Formulations of tranexamic acid which minimize or eliminate the undesirable gastrointestinal side effects in patients on oral tranexamic acid therapy, e.g. women treated for menorrhagia (heavy menstrual bleeding), by modifying the release characteristics of tranexamic acid are disclosed. One embodiment is an extended release formulation, also termed a controlled release formulation, formulated so that the release of tranexamic acid from the dosage form occurs in an extended or controlled fashion to prevent a bolus of tranexamic acid being introduced into the stomach and available for dissolution in the gastric contents. An

alternative embodiment is a delayed release formulation. Delayed release dosage forms are formulated to minimize or prevent the dissolution of the drug in the stomach. The release of tranexamic acid is delayed until the dosage form exits the stomach and reaches the small intestine. Both extended release dosage forms and delayed release dosage forms are termed modified release dosage forms. Such modified release formulations reduce the concentration of tranexamic acid dissolved in the stomach contents. The beneficial effect of this reduced tranexamic acid concentration is to lower the amount of tranexamic acid in the gastric contents so that there are fewer gastric adverse effects with tranexamic acid therapy. This reduction in gastric adverse effects results in improved patient compliance with therapy, because patients will not intentionally miss taking a dose to avoid these adverse side effects. Physicians will also be more likely to initiate and maintain tranexamic acid treatment for their patients because of the reduced patient complaints.

These and other advantages will be apparent in light of the following detailed description and examples.

**DETAILED DESCRIPTION**

The present invention is a modified release tranexamic acid tablet for oral administration. The tablet contains at least one excipient (defined herein as any substance other than the active, i.e., tranexamic acid) which minimizes or eliminates the adverse gastrointestinal side effects in patients, for example, women dosed with oral tranexamic acid for treatment of menorrhagia.

A modified release product is defined by the United States Pharmacopeia (USP) as including delayed release products and extended-(controlled) release products. One embodiment is an extended release formulation,

also called a sustained release formulation or a controlled release formulation. Extended, controlled, or sustained release formulations decrease the concentration of tranexamic acid and excipients dissolved in the stomach fluids after dosing by controllably releasing tranexamic acid over a period of time, as opposed to immediate release formulations which release the entire dose of tranexamic acid all at once. In immediate release formulations the entire dose and the soluble components in the dosage form dissolve in gastric fluid and present a high concentration of solutes for absorption.

Another embodiment is a delayed release formulation. The definition of a delayed release dosage form used herein is that from the USP, Chapter 1151 Pharmaceutical Dosage Forms - Tablets. The tablet contains one or more coatings, intended to delay the release of tranexamic acid until the tablet has passed through the stomach (enteric coatings). A delayed release tablet is a dosage form that releases tranexamic acid at a time later than immediately after administration, that is, it exhibits a lag time in quantifiable plasma tranexamic concentrations. One or more coating(s) delays the release of tranexamic acid until the dosage form has passed through the acidic medium of the stomach.

Delayed release formulations minimize or prevent release of tranexamic acid in the stomach and delay its release until the dosage form has emptied from the stomach into the small intestine. Delayed release formulations include enteric-coated tablets, enteric-coated capsules, enteric-coated granules, and enteric-coated spheres (commonly referred to as "tiny little time pills" or multiparticulate dosage forms).

The enteric coating is stable under the acidic conditions in the stomach and releases tranexamic acid only in the less acidic or substantially neutral medium

of the intestine, (e.g., at pH about 5.5 to about 7.5). It disintegrates, erodes, or dissolves, releasing tranexamic acid only when it encounters the higher pH of the intestine. Enteric-coated formulations substantially prevent dissolution of tranexamic acid in the relatively lower pH of the stomach. Both extended release and delayed release formulations are modified-release forms that thus minimize or prevent gastrointestinal reactions and side effects that occur when a dose of tranexamic acid is ingested and immediately reaches the stomach.

As used herein, the terms extended release formulations, controlled release formulations, or sustained release formulations are used to describe drug product formulations designed to release tranexamic acid over a prolonged period of time. The definition of an extended release tablet used herein is that from the USP, Chapter 1151, as previously cited. The tablet is formulated in such a manner as to make tranexamic acid available over an extended period of time following ingestion. Expressions such as "prolonged action", "repeat-action", and "sustained release" also describe such a dosage form. Extended release dosage forms typically allow reduced dosing frequency as compared to when tranexamic acid is present in an immediate release dosage from. These extended release dosage forms may also reduce fluctuations in plasma tranexamic acid concentrations. Extended release dosage forms may be prepared as a tablet, capsule, granule, pellet or suspension, and may be packaged into capsules, sachets, etc. They may be prepared by any formulation technique where release of the active substance (tranexamic acid) from the dosage form is modified to occur at a slower rate than that from an immediate release product. In these formulations, tranexamic acid release occurs both in the stomach and intestine, but at a slower rate so that a bolus of dissolved drug does not reach the lining of the stomach or intestine and cause adverse effects, or adverse

effects occur with a lower intensity or frequency because of the lower concentration of tranexamic acid. Hence, adverse effects are reduced, minimized or eliminated.

Methods of preparing extended release formulations are known to one skilled in the art and are found in Modified Release Drug Delivery Technology, Rathbone, Hadgraft, and Roberts, Eds., Drugs and the Pharmaceutical Sciences, Vol. 126, Marcel Dekker Inc, New York, 2003; Modern Pharmaceutics, Third Edition, Banker and Rhodes, Eds., Drugs and the Pharmaceutical Sciences, Vol. 72, Marcel Dekker Inc., New York, 1996; Sustained and Controlled Release Drug Delivery Systems, Robinson, Ed., Drugs and the Pharmaceutical Sciences, Vol. 6, Marcel Dekker Inc., NY 1978; Sustained Release Medications, Chemical Technology Review No. 177, Johnson, Ed., Noyes Data Corporation 1980; Controlled Drug Delivery, Fundamentals and Applications, Second Edition, Robinson and Lee, Eds., Marcel Dekker Inc., New York, 1987, and as described in U.S. Patent No. 6,548,084, which is expressly incorporated by reference herein in its entirety. The terms extended release formulation, controlled release formulation, and sustained release formulation are used interchangeably herein, unless indicated otherwise.

An extended release form, one example of a modified release form, makes tranexamic acid available over an extended period of time after ingestion. Extended release dosage forms coupled with the digestion process and the absorption process in the gastrointestinal tract cause a reduction in the amount of tranexamic acid in solution in the gastrointestinal tract compared to dosing tranexamic acid presented as a conventional dosage form (e.g., as a solution, or as an immediate release dosage form). The extended release formulation may be verified by *in vitro* dissolution testing and *in vivo* bioequivalence documentation, according to Food and Drug Administration standards, e.g, as set forth at

www.fda.gov, 21 CFR §314, 320 , and also at USP 23 NF 18 §711, 724. Briefly, *in vitro* dissolution is conducted on twelve individual dosage units. Multipoint dissolution profiles are obtained using discriminating combinations of apparatus, agitation speed, and medium. A surfactant may be used if justified. Sampling times are selected to define the release characteristics of the dosage form and to assure batch to batch reproducibility. Suitable equipment for dissolution testing is specified in USP 23 Apparatus 1 (rotating basket); Apparatus 2 (rotating paddle); Apparatus 3 (reciprocating cylinder*), Apparatus 4 (flow-through cell*); and Apparatus 5 (reciprocating disk*) (*modified testing conditions are used). Rotation speeds of 50 rpm, 100 rpm and 150 rpm are used with baskets, and 50 rpm, 75 rpm and 100 rpm are used with paddles. The temperature is 37°C ± 0.5°C. The dissolution volume is 500 ml to 1000 ml. The dissolution medium is aqueous, at various pH values. The sampling schedule is such that adequate sampling is performed until either 80% of tranexamic acid is released or an asymptote is reached.

Tranexamic acid extended release tablets may be formulated to provide a dose of tranexamic acid, typically 1-2 grams from one to two tablets, within about the first one to two hours after the tablet is ingested. Thus, tranexamic acid release occurs at a controlled rate over an extended period, e.g., about 60 minutes to about 120 minutes. The controlled rate of tranexamic acid release over this period of time is designed to provide a reduced concentration of tranexamic acid in the stomach while allowing the absorption of tranexamic acid to occur throughout the gastrointestinal tract. Absorption of tranexamic acid begins as soon as tranexamic acid is released from the dosage form and is dissolved in the gastrointestinal fluids contacting the membranes which line the gastrointestinal tract. The controlled and extended release of tranexamic acid from the dosage form and the absorption of

drug by the gastrointestinal mucosa help to maintain low concentrations of drug in the gastrointestinal fluids. The lowered concentrations result in lower intensity, frequency, and/or severity of gastrointestinal adverse side effects. The extended release of tranexamic acid from the dosage form in the stomach and the upper small intestine, the natural emptying of gastric juice containing any dissolved tranexamic acid from the stomach, and the absorption of tranexamic acid from a larger segment of the gastrointestinal tract (i.e., both the stomach and the small intestine, rather than the stomach only or the lower portion of the small intestine if an extended release dosage form with a longer release time was used), results in reduced levels of dissolved tranexamic acid in the region of the gastrointestinal tract proximal or distal to the dosage form. Reduced concentrations of tranexamic acid along the gastrointestinal tract reduces adverse gastrointestinal effects associated with oral tranexamic acid therapy.

As used herein, the term delayed release formulation indicates any formulation technique where release of the active substance (tranexamic acid) from the dosage form is modified so that release occurs at a later time than that from a conventional immediate release product. One example of a delayed release formulation is an enteric coated formulation. Enteric coatings on the dosage form are intended to control the region of the gastrointestinal tract where dissolution and subsequent absorption of tranexamic acid from the enteric coated dosage form occurs. Enteric coatings can be prepared to substantially prevent dissolution of the dosage form contents in the stomach. These coatings function by incorporating materials in the enteric coating which allow the enteric coating to remain substantially intact in the acidic environment of the stomach. This substantially intact enteric coating minimizes or prevents the dissolution of tranexamic acid in stomach

contents. Enteric coatings are formulated to release the contents of the dosage form when the pH of the gastrointestinal fluid increases. This increase in pH typically occurs when the dosage form passes out of the stomach into the small intestine. That is, the coating remains intact in the relatively more acidic stomach pH ($pH \leq 2$) and disintegrates, dissolves, or is otherwise removed in the relatively less acidic pH of the intestine ($pH \geq$ about 5 for the upper regions of the small intestine and pH values from about 7 to about 8.5 in the lower regions of the intestines). Formulations can be prepared using enteric coatings intended to release tranexamic acid at pH values of about 5.5 to about 6.5 or at higher pH values that typically occur in the lower regions of the intestines. In those delayed release formulations intended to dissolve at pH 5.5 to about 6.5 or higher, tranexamic acid release occurs substantially only upon reaching the duodenum (the upper portion of the small intestine) so that substantially no tranexamic acid is released in the stomach, thus minimizing or eliminating adverse effects.

Tranexamic acid formulated as delayed release tablets may contain an enteric coating which disintegrates, dissolves, or erodes at neutral or slightly acidic or slightly alkaline pH, and thereby allows dissolution of tranexamic acid upon leaving the stomach, that is, upon stomach emptying into the small intestine. The release of tranexamic acid in the intestine reduces gastrointestinal side effects associated with the large dose of tranexamic acid quickly released into the stomach. Patients treated with enteric coated formulations of tranexamic acid for delayed release should be cautioned to not consume antacids while under tranexamic therapy, because antacids will change the stomach pH and thus alter the site of tablet dissolution or disintegration. Other types of delayed release formulations are available, and the above example is not limiting.

A delayed release form, another example of a modified release form, makes tranexamic acid available at a time other than immediately following oral administration. As for extended release formulations, delayed release formulations may be verified by *in vitro* dissolution testing and *in vivo* bioequivalence documentation according to the standard available as previously set forth (USP 23 NF 18, §§711, 724). When the guidance refers to dissolution testing in addition to application/compendial release requirements, the dissolution test should be performed in 0.1 N HCl for two hours (acid stage), followed by testing in USP buffer media at a pH range between 4.5 to 7.5 (buffer stage) under standard (application/compendial) test conditions and increased agitation speeds using the application/compendial test apparatus. For the rotating basket method (Apparatus 1) a rotation speed of 50 rpm, 100 rpm, and 150 rpm may be used, and for the rotating paddle method (Apparatus 2) a rotation speed of 50 rpm, 75 rpm, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, e.g., at 15 min, 30 min, 45 min, 60 min, 120 min (following the time from which the dosage form is placed in the buffer), until either 80% of the drug is released or an asymptote is reached.

Methods of preparing delayed release formulations are known to one skilled in the art and are found in, for example, Remington's Pharmaceutical Sciences 16$^{th}$ Edition, Mack Publishing Company 1980, Osol, Ed., and the references cited for extended release formulations.

As used herein, alleviation of adverse effects using these formulations indicates any relief in one or more symptoms, such as decrease in incidence, severity, or duration of symptoms, and is not limited to absence of symptoms or elimination of symptoms. Thus, treatment includes any decrease in incidence,

duration, intensity, frequency, etc. of adverse gastrointestinal symptoms including, but not limited to, nausea, bloating, cramping, vomiting, diarrhea, and constipation. The formulations may reduce symptoms at any time during tranexamic acid therapy, but minimized adverse effects are particularly noted immediately or shortly after dosing, that is, within the first few hours after dosing. As used herein, adverse gastrointestinal effects and side effects are used interchangeably to indicate non-therapeutic effects (i.e., not relating to any possible beneficial effects due to tranexamic acid), ranging from unpleasant but tolerable sensations to severe gastrointestinal symptoms. As used herein, the terms oral formulations, ingestable formulations, and orally administered formulations are used interchangeably and include any dosage forms which are ingested by mouth, including, but not limited to, tablets, pills, liquids, gelcaps, dragees, capsules, powders, granules, pellets, etc.

Delayed release formulations may be enteric coated tranexamic acid tablets or enteric coated granules. These tablets may be prepared by coating compressed tablets with a commercial or specially formulated enteric film coat, for example, a wax, polymer, and/or a pH-sensitive matrix that meets (USP) and Food and Drug Administration (FDA) requirements for enteric coated tablets. The enteric coating permits disintegration of the tranexamic acid tablets and dissolution of tranexamic acid as a result of the pH change between the stomach and the duodenum. Tablet excipients which inhibit rapid release of tranexamic acid in the stomach and which promote dissolution and release in the intestine may also be used. These include, but are not limited to, phthalic acid derivatives such as phthalic acid derivatives of vinyl polymers and copolymers, hydroxyalkylcelluloses, alkylcelluloses, cellulose acetates, hydroxyalkylcellulose acetates, cellulose ethers, alkylcellulose acetates and partial esters thereof, and polymers and copolymers of

lower alkyl acrylic acids and lower alkyl acrylates and partial esters thereof. Commercial preparations intended for the enteric coating of tablets, capsules, and granules are available from Degussa (Parsippany, NJ) and Colorcon (West Point, PA). In one embodiment, the polymers are methacrylic acid copolymers. These are copolymers of methacrylic acid with neutral acrylate or methacrylate esters such as ethyl acrylate or methyl methacrylate, for example, methacrylic acid copolymer, Type C, USP (a copolymer of methacrylic acid and ethyl acrylate having between 46.0% and 50.6% methacrylic acid units), commercially available from Rohm Pharma as Eudragit® L 100-55 (as a powder) or L30D-55 (as a 30% dispersion in water). In another embodiment, the polymers are hydroxypropyl cellulose phthalate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, polyvinylacetate phthalate, polyvinylpyrrolidone phthalate, and the like. One or more pH-dependent excipient(s) are present in amounts ranging from about 1% by weight to about 20% by weight, from about 5% by weight to about 12% by weight, or in an amount of about 10% by weight.

The quantity of pH dependent excipients is sufficient to produce a delayed release formulation from which the release rate of tranexamic acid is controlled such that at a pH below about 5 the rate of dissolution is significantly retarded. For methacrylic acid copolymer, type C, USP (Eudragit® L 100-55), a quantity of pH dependent polymer coating may be applied to tablets in the range between about 2% to about 15% by weight (dry basis). In another embodiment, the range is between about 3% to about 6% by weight (dry basis). The pH dependent polymer may have from about 1% to about 20% of the methacrylic acid carboxyl groups neutralized. In one embodiment about 3% to about 6% of the binder methacrylic acid carboxyl groups are neutralized. One or more pH independent

excipients may be present in amounts ranging from about 1% by weight to about 10% by weight, from about 1% by weight to about 3% by weight, or in an amount of about 2% by weight. Film-forming or viscosity enhancing agents may also be present, such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, polyvinylpyrrolidone, neutral poly(meth)acrylate esters, and the like.

Excipients may be admixed so as to form a homogeneous mixture with tranexamic acid and the pH dependent binder. Excipients include pH independent binders or film-forming agents such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, polyvinylpyrrolidone, neutral poly(meth)acrylate esters (e.g., the methyl methacrylate/ethyl acrylate copolymers sold as Eudragit® (Rohm Pharma), starches, gelatin, sugars such as glucose, sucrose, and mannitol, silicic acid, carboxymethylcellulose, and the like, diluents such as lactose, mannitol, dry starch, microcrystalline cellulose and the like, surface active agents such as polyoxyethylene sorbitan esters, sorbitan ethers, and the like, coloring agents, flavoring agents, lubricants such as talc, calcium stearate, and magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and other tableting aids. These excipients may be combined with tranexamic acid to form delayed release tablets.

In one embodiment of tranexamic tablets, tranexamic acid is in the range of about 50% by weight to about 95% or more by weight. In other embodiments, tranexamic acid is in the range of about 70% by weight to about 90% by weight, or about 70% by weight to about 80% by weight. The pH dependent binder may be in the range of about 5% by weight to about 40% by weight, about 5% by weight to about 25% by weight, or about 5% by weight to about 15% by weight. The remaining weight may be made up of pH independent binders, fillers, or other excipients.

To prepare delayed release tablet formulations, the agent to control the release of tranexamic acid may be incorporated into the tablet matrix or coated onto the tablet surface or both. Tablet formulations prepared with the pH dependent excipient added as a binder in the tablet matrix are formulated by granulating a blend of powders composed with the pH dependent binder. Alternatively, the pH dependent binder may be added as a powder and wet granulated by addition of a solvent to the powder blend. The powder blend is formed by combining portions of the powdered components that make up the tablet. These powders are intimately mixed by dry-blending. The dry blended mixture is granulated by wet mixing of a solution of a binding agent with the powder blend. The time for such wet mixing may be controlled to influence the dissolution rate of the formulation. For example, the total powder mix time, that is, the time during which the powder is granulated, may range from about 1 min to about 10 min, or from about 2 min to about 5 min. Following granulation, the particles are removed from the granulator and placed in a fluid bed dryer, a vacuum dryer, a microwave dryer, or a tray dryer for drying. Drying conditions are sufficient to remove unwanted granulating solvent, typically water, or to reduce the amount of granulating solvent to an acceptable level. Drying conditions in a fluid bed dryer or tray dryer are typically about 60°C. The granulate is dried, screened, mixed with additional excipients such as disintegrating agents, flow agents, or compression aids and lubricants such as talc, stearic acid, or magnesium stearate, and compressed into tablets.

The tablet that contains a delayed release agent within the tablet matrix may be coated with an optional film-forming agent. This applied film may aid in identification, mask an unpleasant taste, allow desired colors and surface appearance, provide enhanced elegance, aid in swallowing, aid in enteric coating,

etc. The amount of film-forming agent may be in the range of about 2% tablet weight to about 4% tablet weight. Suitable film-forming agents are known to one skilled in the art and include hydroxypropyl cellulose, cellulose ester, cellulose ether, one or more acrylic polymer(s), hydroxypropyl methylcellulose, cationic methacrylate copolymers (diethylaminoethyl) methacrylate/methyl-butyl-methacrylate copolymers such as Eudragit E® (Rohm Pharma) and the like, The film-forming agents may optionally contain colorants, plasticizers, fillers, etc. including, but not limited to, propylene glycol, sorbitan monooleate, sorbic acid, titanium dioxide, and one or more pharmaceutically acceptable dye(s).

In one embodiment, tranexamic acid tablets are coated with an enteric film coat. Tranexamic acid tablets are formulated by dry blending, rotary compacting, or wet granulating powders composed of tranexamic acid and tablet excipients. These powders are compressed into an immediate release tablet. Coating this immediate release tablet with an enteric coating renders this tranexamic acid tablet as a delayed release tablet.

Extended release formulations of tranexamic acid include tablets, pellets, granules, capsules, or other oral dosage forms prepared in such a way to release tranexamic acid in a controlled manner.

Extended release tranexamic acid tablets are prepared by adding a gel- forming or hydratable polymer to a tranexamic tablet composition. Suitable gel-forming or hydratable polymers include, but are not limited to, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, polyvinyl alcohol, etc. This provides a compressed tablet that may or may not be film-coated. The tablet releases tranexamic acid by diffusion of tranexamic acid through the tablet matrix, or by erosion of the tablet matrix, or by a combination of

diffusion from and erosion of the tablet matrix. Alternatively, water-swellable polymers may be used to form the tablet matrix. Tablets formed with water swellable polymers release tranexamic acid by diffusion of tranexamic acid through the tablet matrix, or by erosion of the tablet matrix, or by a combination of diffusion from and erosion of the tablet matrix. One or more water-soluble hydrophilic polymer(s) may also be used. These include polyvinylpyrrolidine, hydroxypropyl cellulose, hydroxypropylmethylcellulose, now referred to as hypromellose (e.g., Methocel™, Dow Chemical Company), methyl cellulose, vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers, derivatives thereof and mixtures thereof. In various embodiments, the polymer is hydroxypropyl cellulose or hydroxypropylmethylcellulose. The polymer may be hydroxypropyl-methyl cellulose with a viscosity ranging from about 50 cps to about 200 cps. The polymer may be hydroxypropylmethylcellulose with a viscosity of 100 cps, commercially available as Methocel™ K 100 LV (Dow Chemical Company). The amount of polymer in the composition may be in the range of about 5% by weight to about 50% by weight of the composition. In various embodiments, the polymer is in the range of about 10% by weight to about 35% by weight of the composition, or about 10% by weight to about 30% by weight of the composition.

The tablet matrix may also contain soluble and insoluble components to aid in the formulation and/or the extended release rate of tranexamic acid. The release process may be adjusted by varying the type, amount, and the ratio of the tablet ingredients to produce the desired dissolution profile, as known to one skilled in the art. A coating may be a partially neutralized pH-dependent binder that controls the rate of tranexamic acid dissolution in aqueous media across the range of pH in the stomach, which has a pH of about 2, and the intestine, which has a pH of about

5.5. One or more pH dependent binders are used to control the dissolution profile so that tranexamic acid is released slowly and continuously as the formulation passes through the stomach and gastrointestinal tract.

In one embodiment, compressed extended release tablets are formulated to comply with USP criteria and to be of such a size and shape to be easy to swallow. The size of the tablet will depend upon the dose of tranexamic acid that is needed to provide adequate therapy and the particular formulation and excipients that are selected to provide the physical properties necessary for tableting and for extended release. In various embodiments, a compressed extended release tablet contains from about 500 mg to about 1 gram of tranexamic acid, or from about 600 mg to about 750 mg of tranexamic acid. The daily dose of tranexamic acid may be achieved by taking one or two tablets at each dosing time.

In one embodiment, the dose of tranexamic acid per tablet is in the range of about 500 mg to about 1000 mg for tablets and from about 500 mg to about 1500 mg for a sachet filled with granules. In another embodiment, the dose of tranexamic acid is in the range of about 3 grams/day to about 6 grams/day in three or four divided doses. As an example, a total daily dose of 3 grams tranexamic acid may be divided into three doses of one tablet each with each tablet containing 1 gram tranexamic acid, or may be divided into four doses of one tablet each with each tablet containing 0.775 gram tranexamic acid. As another example, a total daily dose of 4 gram tranexamic acid may be divided into three doses of two tablets at each dose with each tablet containing 0.666 gram tranexamic acid, or may be divided into four doses of one tablet each with each tablet containing 1 gram tranexamic acid. As another example, a total daily dose of 5 gram tranexamic acid may be divided into three doses of one tablet each with each tablet containing 0.833

gram tranexamic acid, or may be divided into four doses of two tablets each with each tablet containing 0.625 gram tranexamic acid. As another example, a total daily dose of 6 gram tranexamic acid may be divided into three doses of two tablets each with each tablet containing 1 gram tranexamic acid, or may be divided into four doses of two tablets each with each tablet containing 0.75 gram tranexamic acid. For ease of swallowing, the dose of tranexamic acid taken at each dosing time may be delivered by taking multiple tablets. For example, the 4 gram daily dose may be delivered by taking two 666.67 mg tablets three times a day or two 500 mg tablets four times a day. Similarly, the 3 gram daily dose may be achieved by taking two 550 mg tablets three times a day or two 375 mg tablets four times a day. Alternatively, for ease of reference, a dose of 600 mg, 650 mg, or 700 mg of tranexamic acid per tablet may be used. Alternatively, each dose may be delivered by taking granules containing the prescribed amount of tranexamic acid presented in a convenient unit dose package. Such examples are not limiting and other doses within these ranges will be appreciated by those skilled in the art.

Alternatively, extended release or delayed release tranexamic acid formulations may be administered by pellets or granules in a sachet. Extended release tranexamic acid pellets or granules may be prepared by using excipients to control the release of tranexamic acid from the granule or pellet matrix. Extended release preparations may also be formulated using coatings to control the release of tranexamic acid from the granule or pellet. Delayed release formulations may be prepared by incorporating excipients to control the release of tranexamic acid in the matrix of the granule or pellet, or as coating materials on the surface of the granule or pellet. U.S. Patent No. 6,433,215, which is expressly incorporated by reference herein in its entirety, discloses a method of building layers of drug and binder on

sugar spheres and coating them with a membrane to form a film coating. Such a coating may be used for either an extended release formulation or a delayed release formulation, and/or for pharmaceutical elegance. U.S. Patent Nos. 5,650,174; 5,229,135; and 5,242,337, each of which is expressly incorporated by reference herein in its entirety, disclose variations on fabricating a pellet or nonpareil dosage form. Spheres are filled into packets, termed sachets, which are filled by weight to contain the prescribed dose of drug. Multiparticulates may be coated with an extended release coating or a delayed release coating, as disclosed in U.S. Patent No. 6,066,339, which is expressly incorporated by reference herein in its entirety. Coated multiparticulates may be packaged in capsules or sachets. The formulation of granules or pellets for extended or delayed release is described in Multiparticulate Oral Drug Delivery, Ghebre-Sellassie, Ed. in Drugs and the Pharmaceutical Sciences, Vol. 65, Marcel Dekker Inc., NY, 1994 and in the relevant parts of the references for extended release formulations and delayed release formulations previously cited and the relevant portions incorporated herein by reference.

The inventive tranexamic acid formulations may be used for additional indications other than menorrhagia.

The invention will be further appreciated with respect to the following examples.

**EXAMPLE 1**

A sustained release formulation includes pH-dependent and -independent binders. Tranexamic acid (5333 g) is combined with methacrylic acid copolymer, Type C (Eudragit® L 100-55 (Rohm Pharma) (200 g), microcrystalline cellulose (Avicel®) (142 g), and polyvinyl pyrrolidone powders (20 g) and intimately mixed in a Fielder PMA 65 mixer-granulator. The mixture is granulated with a

solution of sodium hydroxide (8 g) in water, and a 30% aqueous dispersion of methyl methacrylate/ethyl acrylate copolymer (Eudragit® NE 30 D (Rohm Pharma) (300 g) is added to the wet mass. The resulting granulate is dried in an Aeromatic Strea-5 fluid bed drier, screened, and then mixed with croscarmellose sodium (10 g) and magnesium stearate (10 g). The mixture is compressed into tablets with a Manesty B tablet press to achieve a dose of 700 mg tranexamic acid per tablet.

**EXAMPLE 2**

A sustained release formulation is prepared according to Example 1 except that Eudragit® L 100-55 is reduced to 100 g, and Eudragit® NE 30 D is replaced by a 40% aqueous dispersion of a methyl methacrylate/ethyl acrylate copolymer (Eudragit® NE 40 D (Rohm Pharma) 200 g).

**EXAMPLE 3**

A sustained release formulation is prepared by blending tranexamic acid 700 mg/tablet with microcrystalline cellulose and polyvinylpyrrolidine K25, granulating with water, drying, and blending with croscarmellose sodium and magnesium stearate. The blend is compressed into tablets and coated with an enteric coating.

**EXAMPLE 4**

An extended release composition is prepared by mixing tranexamic acid (3000 g) and from about 100 g to about 300 g Methocel™ K 100 LV (Dow Chemical Company). The mixture is dry blended, and then is granulated using water until proper granulation is obtained, as known to one skilled in the art. Wet granules are dried in a fluid bed dryer, sifted, and ground to appropriate size. Lubricating and flow agents are mixed with the dried granulation to obtain a final formulation which is compressed into tablets containing 650 mg of tranexamic acid per tablet.

**EXAMPLE 5**

Methocel™ K 100 LV (Dow Chemical Company) is loaded into a mixer and dry blended with tranexamic acid. The mixture is granulated using water until proper granulation is obtained, as known to one skilled in the art. The granulation is then dried, sifted, and ground to appropriate size.

Talc and magnesium stearate are screened and blended with dry granulation. The granulation is loaded into a hopper and compressed into tablets. Tablets are then coated with an aqueous film coating.

In the following formulations, 650 mg tranexamic acid tablets are compressed from the granulation with water added up to the desired quantity (qs).

Formulation one contains 50 mg/tablet Methocel™ K 100 LV Premium CR Grade (Dow Chemical Company), 50 mg/tablet lactose monohydrate, 25 mg/tablet USP talc, and 8 mg/tablet magnesium stearate.

Formulation two contains 75 mg/tablet Methocel™ K 100 LV Premium CR Grade (Dow Chemical Company), 50 mg/tablet lactose monohydrate, 25 mg/tablet USP talc, and 10 mg/tablet magnesium stearate.

Formulation three contains 100 mg/tablet Methocel™ K 100 LV Premium CR Grade (Dow Chemical Company), 50 mg/tablet lactose monohydrate, 30 mg/tablet USP talc, and 10 mg/tablet magnesium stearate.

Other variations or embodiments of the invention will also be apparent to one of ordinary skill in the art from the above descriptions and examples. Thus, the forgoing embodiments are not to be construed as limiting the scope of this invention.

What is claimed is: